and harmless buffer substances and a tonicity adjusting agent. Each milliliter contains cefmetazole sodium equivalent to 20 milligrams or 40 milligrams of cefmetazole per milliliter. Its cefmetazole content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefmetazole that it is represented to contain. It is sterile. It contains not more than 0.2 endotoxin units per milligram. Its pH is not less than 4.2 and not more than 6.2. It passes the identity test. The cefmetazole used conforms to the standards prescribed by §442.69(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The cefmetazole used in making the batch for potency, moisture, and identity.

(B) The batch for potency, sterility, bacterial endotoxins, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The cefmetazole used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch:

(*1*) For all tests except sterility: A minimum of 12 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay.* Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) *Cefmetazole potency.* Proceed as directed in §442.70a(b)(1), except prepare the sample solution and calculate the cefmetazole content as follows:

(i) *Preparation of sample solution.* Using a suitable hypodermic needle and syringe, remove an accurately measured portion from each container immediately after thawing and reaching room temperature and dilute with mobile phase to obtain a solution containing 500 micrograms of cefmetazole per milliliter (estimated). Prepare the sample solution just prior to its introduction into the chromatograph.

(ii) *Calculation.* Calculate the milligrams of cefmetazole per milliliter of sample as follows:

$$\text{Milligrams of cefmetazole per milliliter} = \frac{A_U \times P_s \times d}{A_s \times 1{,}000}$$

where:

A_U=Area of the cefmetazole peak in the chromatogram of the – sample (at a retention time equal to that observed for the standard);

A_S=Area of the cefmetazole peak in the chromatogram of the cefmetazole working standard;

P_S=Cefmetazole activity in the cefmetazole working standard solution in micrograms per milliliter; and

d = Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Bacterial endotoxins.* Proceed as directed in the United States Pharmacopeia bacterial endotoxins test.

(4) *pH.* Proceed as directed in §436.202 of this chapter, using the undiluted solution.

(5) *Identity.* The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefmetazole working standard.

[59 FR 12546, Mar. 17, 1994]

PART 443—CARBACEPHEM ANTIBIOTIC DRUGS

Subpart A—Bulk Drugs

Sec.
443.20 Loracarbef.

Subpart B—Oral Dosage Forms

443.120 Loracarbef oral dosage forms.
443.120a Loracarbef capsules.
443.120b Loracarbef for oral suspension.

AUTHORITY: Sec. 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357).

SOURCE: 58 FR 26667, May 4, 1993, unless otherwise noted.

Subpart A—Bulk Drugs

§ 443.20 Loracarbef.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Loracarbef is the monohydrate form of (6*R*,7*S*)-7-[(*R*)-2-amino-2-phenylacetamido]-3-chloro-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 960 micrograms and not more than 1,020 micrograms of loracarbef activity per milligram, on an anhydrous basis.

(ii) Its moisture content is not less than 3.5 percent and not more than 6.0 percent.

(iii) The pH of an aqueous slurry containing 100 milligrams per milliliter is not less than 3.5 and not more than 5.5.

(iv) Its specific rotation in an 0.1 *N* HCl solution containing 10 milligrams of loracarbef per milliliter at 25° C is +27° to +33° on an anhydrous basis.

(v) It is crystalline.

(vi) It gives a positive identity test.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for loracarbef potency, moisture, pH, specific rotation, crystallinity, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 265 nanometers, a 25-centimeter by 4.6-millimeter (inside diameter) column packed with microparticulate (5 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded to silicas, a flow rate of 1.5 milliliters per minute, and a known injection volume between 10 and 20 microliters. The retention time for loracarbef is between 10 and 13 minutes. Mobile phase, working standard, sample and resolution test solutions, system suitability requirements, and calculations are as follows:

(i) *Mobile phase.* Dissolve 2.0 grams of pentanesulfonic acid sodium salt monohydrate in 1,560 milliliters of water. Add 20 milliliters of triethylamine. Adjust the pH to 2.5 with phosphoric acid. Add 440 milliliters of methanol and mix. Filter the mobile phase through a suitable filter capable of removing particulate matter 0.5 micron in diameter and degas it just prior to its introduction into the chromatograph.

(ii) *Preparation of working standard, sample, and resolution test solutions*—(A) *Working standard solution.* Accurately weigh approximately 10 milligrams of the loracarbef working reference standard into a 50-milliliter volumetric flask. Dissolve and dilute to volume with mobile phase. Brief sonication may be required to obtain complete dissolution of the material.

(B) *Sample solution.* Accurately weigh approximately 10 milligrams of sample into a 50-milliliter volumetric flask. Dissolve and dilute to volume with mobile phase. Brief sonication may be required to obtain complete dissolution of the material.

(C) *Resolution test solution.* Prepare a resolution test solution containing approximately 0.2 milligram per milliliter each of loracarbef and loracarbef *L*-isomer in the mobile phase.

(iii) *System suitability requirements*—(A) *Asymmetry factor.* The asymmetry factor (A_S) at 5 percent peak height is satisfactory if it is not less than 0.8 and not more than 1.3 for the loracarbef peak.

(B) *Efficiency of the column.* The absolute efficiency (h_r) is satisfactory if it is not more than 20 for the loracarbef peak.

(C) *Resolution factor.* The resolution factor (R) between the peak for loracarbef and the peak for the resolution standard loracarbef *L*-isomer in the resolution test solution is satisfactory if it is not less than 6.0.

(D) *Coefficient of variation (relative standard deviation).* The coefficient of variation (S_R in percent of 5 replicate injections) is satisfactory if it is not more than 2.0 percent.

(E) *Capacity factor (k′).* The capacity factor (k') for loracarbef is satisfactory

if it is not less than 5 and not more than 8.

If the system suitability parameters have been met, then proceed as described in §436.216(b) of this chapter.

(iv) *Calculations.* Calculate the micrograms of loracarbef per milligram of sample on an anhydrous basis as follows:

$$\text{Micrograms of loracarbef per milligram} = \frac{A_U \times P_s \times 100}{A_s \times C_U \times (100 - m)}$$

where:

A_U=Area of the loracarbef peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_S=Area of the loracarbef peak in the chromatogram of the loracarbef working standard;

P_S=Loracarbef activity in the loracarbef working standard solution in micrograms per milliliter;

C_U=Milligrams of sample per milliliter of sample solution; and

m = Percent moisture content of the sample.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous suspension containing 100 milligrams per milliliter.

(4) *Specific rotation.* Dissolve and dilute an accurately weighed sample with sufficient 0.1 *N* HCl to obtain a concentration of approximately 10 milligrams of loracarbef activity per milliliter. Proceed as directed in §436.210 of this chapter, using a 1.0-decimeter polarimeter tube. Calculate the specific rotation on the anhydrous basis.

(5) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

(6) *Identity.* Proceed as directed in §436.211 of this chapter, using the 1.0 percent potassium bromide disc prepared as described in §436.211(b)(1).

Subpart B—Oral Dosage Forms

§443.120 Loracarbef oral dosage forms.

§443.120a Loracarbef capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Loracarbef capsules are composed of loracarbef and one or more suitable and harmless lubricants and diluents enclosed in a gelatin capsule. Each capsule contains loracarbef equivalent to either 200 milligrams or 400 milligrams of loracarbef. Its loracarbef content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of loracarbef that it is represented to contain. Its moisture content is not more than 8.5 percent. It passes the dissolution test. It passes the identity test. The loracarbef used conforms to the standards prescribed by §443.20(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The loracarbef used in making the batch for potency, moisture, pH, specific rotation, crystallinity, and identity.

(B) The batch for content, moisture, dissolution, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The loracarbef used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch: A minimum of 100 capsules.

(b) *Tests and methods of assay*—(1) *Loracarbef content.* Proceed as directed in §443.20(b)(1), preparing the sample solution and calculating the loracarbef content as follows:

(i) *Preparation of sample solution.* Place one intact capsule in a 200-milliliter volumetric flask containing 150 milliliters of distilled water. Shake the mixture vigorously to aid disruption of the capsule. Sonicate the mixture briefly (5 minutes). Dilute the contents to volume with distilled water. Mix well and immediately transfer a suitable aliquot to a volumetric flask of appropriate size to obtain a solution containing 0.2 milligram per milliliter (estimated) of loracarbef when diluted to volume with mobile phase (described in §443.20(b)(1)(i)). Filter this solution through a 0.45-micron membrane filter

before injecting it into the chromatograph.

(ii) *Calculations.* Calculate the loracarbef content as follows:

$$\text{Milligrams of loracarbef per capsule} = \frac{A_U \times P_s \times d}{A_s \times 1{,}000}$$

where:

A_U=Area of the loracarbef peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_S=Area of the loracarbef peak in the chromatogram of the loracarbef working standard;

P_S=Loracarbef activity in the loracarbef working standard solution in micrograms per milliliter; and

d = Dilution factor of the sample.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Dissolution test.* Proceed as directed in § 436.215 of this chapter. The quantity Q, the amount of loracarbef activity dissolved, is 75 percent within 30 minutes.

(4) *Identity.* The retention time of the loracarbef response in the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section as applied to the sample solution compares qualitatively to that of the loracarbef reference standard.

§ 443.120b Loracarbef for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Loracarbef for oral suspension is loracarbef with one or more suitable and harmless preservatives, sweeteners, suspending agents, colorings, antifoaming agents, and flavorings. When constituted as directed in the labeling, each milliliter contains the equivalent of either 20 or 40 milligrams loracarbef activity. Its loracarbef content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of loracarbef that it is represented to contain. Its moisture content is not more than 2.0 percent. When constituted as described in the labeling, the pH of the suspension is not less than 3.5 and not more than 6.0. It passes the identity test. The loracarbef used conforms to the standards prescribed by § 443.20(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The loracarbef used in making the batch for potency, moisture, pH, specific rotation, crystallinity, and identity.

(B) The batch for content, moisture, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The loracarbef used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch: A minimum of 10 immediate containers.

(b) *Tests and methods of assay*—(1) *Loracarbef content.* Proceed as directed in § 443.20(b)(1), preparing the sample solution and calculating the loracarbef content as follows:

(i) *Preparation of sample solution.* Constitute as directed in the labeling. Transfer a 5.0-milliliter portion of the suspension into an appropriately sized volumetric flask and quantitatively dilute stepwise with mobile phase (described in § 443.20(b)(1)(i)) to obtain a concentration of 0.2 milligram of loracarbef activity per milliliter (estimated).

(ii) *Calculations.* Calculate the loracarbef content as follows:

$$\text{Milligrams of loracarbef per 5 milliliters of sample} = \frac{A_U \times P_s \times d}{A_s \times 1{,}000}$$

where:

A_U=Area of the loracarbef peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_S=Area of the loracarbef peak in the chromatogram of the loracarbef working standard;

P_S=Loracarbef activity in the loracarbef working standard solution in micrograms per milliliter; and

d = Dilution factor of the sample.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the drug constituted as directed in the labeling.